

(16)

## PATENT ABSTRACTS OF JAPAN

(11)Publication number : 2003-175320

(43)Date of publication of application : 24.06.2003

(51)Int.Cl. B01D 69/08  
B01D 61/24  
B01D 63/02  
B01D 67/00  
B01D 71/44  
B01D 71/68

(21)Application number : 2002-292729

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(22)Date of filing : 04.10.2002

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(30)Priority

Priority number : 2001309673 Priority date : 05.10.2001 Priority country : JP

## (54) METHOD FOR MANUFACTURING HOLLOW FIBER MEMBRANE

(57)Abstract:

PROBLEM TO BE SOLVED: To provide a method for obtaining a hollow fiber membrane especially reduced in the irregularity of capacity such as water penetration quantity, water permeability or the like in a method for manufacturing a dry membrane extremely reduced in the elution quantity from the membrane and having excellent dialyzing capacity reduced in the adhesion of blood protein or a platelet.

SOLUTION: A method for manufacturing the dry hollow fiber membrane reduced in the amount of an eluted substance includes a process wherein a wet membrane comprising a polysulfone polymer and polyvinylpyrrolidone and containing no membrane pore holding material high in water penetration quantity and having a large pore size is preliminarily manufactured and dried after desolvation to contract the pore size of the wet membrane and a part of polyvinylpyrrolidone in the membrane is further made insoluble in water. In this manufacturing method, the wet membrane drying process is performed by the irradiation with microwaves. A module comprising the hollow fiber membrane obtained by this manufacturing method is also disclosed.

## LEGAL STATUS

[Date of request for examination] 18.08.2005

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision]

of rejection]

[Date of requesting appeal against examiner's  
decision of rejection]

[Date of extinction of right]

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CLAIMS

[Claim(s)]

[Claim 1] The humid film which does not contain the pit maintenance material of a big aperture in the amount of high water penetration which consists of a polysulfone system polymer and a polyvinyl pyrrolidone is manufactured beforehand. After shrinking the aperture of this humid film by drying after desolvation, include the process which insolubilizes a part of polyvinyl pyrrolidone in the film in water further. The manufacture approach of the hollow filament-like film which is the approach of manufacturing the dry hollow filament-like film with few effluents, and is characterized by performing the desiccation process of the humid film by microwave exposure.

[Claim 2] The manufacture approach according to claim 1 characterized by \*\*\*\*(ing) the hollow filament-like film in the shape of a thread at the time of desiccation, and ventilating a dehumidification gas in this thread.

[Claim 3] The manufacture approach according to claim 2 characterized by the difference of the water content of the film in the core and the periphery section of a thread at the time of desiccation initiation being less than 10%.

[Claim 4] The manufacture approach according to claim 2 or 3 characterized by reducing the output of a microwave exposure when the average water content of a thread becomes 20 - 70% after desiccation initiation.

[Claim 5] The manufacture approach according to claim 2 or 3 characterized by changing from microwave exposure desiccation to with a 40-degree-C or more temperature [ temperature 120 degrees C or less ] stoving when the average water content of a thread becomes 20 - 70% after desiccation initiation.

[Claim 6] The manufacture approach according to claim 4 or 5 characterized by the difference of the water content of the film in the core and the periphery section of this thread in the time of the average water content of the thread after desiccation initiation becoming 20 - 70% being less than 5%.

[Claim 7] The manufacture approach according to claim 1 to 6 characterized by the ratio of the polyvinyl pyrrolidone to a polysulfone system polymer being 18 - 27 % of the weight by a film production undiluted solution consisting of a polysulfone system polymer, a polyvinyl pyrrolidone, and a solvent.

[Claim 8] The module which consists of hollow filament-like film manufactured by the approach according to claim 1 to 7.

[Claim 9] The module according to claim 8 which is an object for hemodialysis.

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## DETAILED DESCRIPTION

### [Detailed Description of the Invention]

[0001]

[Field of the Invention] This invention has very few elution volumes from the film, and adhesion of blood protein and a platelet is related with the approach of manufacturing the small hollow filament-like film of dispersion in engine performance, such as the amount of water penetration, and permeability, especially, in the manufacture approach of the high performance hollow filament-like film of having little outstanding dialysis engine performance. Moreover, this invention relates also to the module which consists of hollow filament-like film manufactured such.

[0002]

[Description of the Prior Art] The technique of using the film which has alternative permeability progresses splendidly in recent years, and utilization in extensive fields, such as a separation filter of a gas or a liquid, hemodialyzer in the medical field, a hemofiltration machine, and a constituent-of-blood selection separation filter, is progressing until now. As an ingredient of this film, polymers, such as cellulose systems (a regenerated-cellulose system, a cellulose acetate system, chemistry denaturation cellulose system, etc.), a polyacrylonitrile system, a polymethylmethacrylate system, a polysulfone system, a polyethylene vinyl alcohol system, and a polyamide system, have been used. Among these, since haemocompatibility of a polysulfone system polymer improves by in addition to the thermal stability, acid-proof, and alkali resistance adding a hydrophilization agent to a film production undiluted solution, and producing a film to it, it was observed as a semipermeable membrane material and research has been advanced.

[0003] On the other hand, in order to paste up the film and to produce a module, it is necessary to dry the film but, and if the porous film which consists of an organic macromolecule, the permeable membrane which consists of hydrophobic polymers, such as a polysulfone system, especially, and ultrafiltration membrane are dried after film production, it is known that the amount of water penetration will fall remarkably compared with desiccation before. Therefore, the film always needed to be dealt with in the damp or wet condition and the condition of having made water immersed.

[0004] The approach conventionally taken as this cure was putting low volatility organic liquids, such as a glycerol, in the hole part in the porous film after film production and before desiccation. However, since hyperviscosity [ a low volatility organic liquid ] generally, although washing removal took time amount, module molding of the film was carried out and after washing was a minute amount, the problem was to see the effluent of the low volatility organic liquid origin etc. in module mounting fluid (various derivatives which reacted chemically with the low volatility organic liquid, and were generated).

[0005] Although the method of using the mineral salt of a calcium chloride etc. instead of a low volatility organic liquid is shown in the patent reference 1 as an approach of drying without using a low volatility organic liquid, there is no change in the need of carrying out washing removal. Moreover, though it is a minute amount, it is apprehensive about the bad influence which the mineral salt which remained has on a dialysis patient.

[0006] Moreover, the manufacture approach of the hollow fiber which irradiates microwave is

shown in the patent reference 2 as the membranous desiccation approach, performing moist heat treatment by the steam to a hollow fiber. However, since steam treatment is carried out in order to prevent deformation of the film, though it is desiccation, there is a fault which lengthens the drying time, and further, since it is the desiccation after making low volatility organic liquids, such as a glycerol, adhere, the purpose of reducing the effluent from the film is not attained.

[0007] The hydrophilization film containing the polyvinyl pyrrolidone which carried out desiccation processing to the patent reference 3 and the patent reference 4, without using a low volatility organic liquid is indicated. Although the engine performance which separates a plasma component from blood is indicated by these, since plasma protein penetrates, it turns out that it is not effective as permeable membrane. Moreover, since the polyvinyl pyrrolidone is dried at the temperature decomposed and denatured, in the purpose of reducing the effluent from the film, it is the process which is not very desirable.

[0008] Moreover, the hollow fiber to which blood made abundance of the polyvinyl pyrrolidone in the film internal surface which contacts directly about 20 - 50% is indicated by the patent reference 5. This shows the humid film for mainly lessening affixes, such as blood protein and a platelet. Therefore, although it is shown that change cannot take place easily at the time of the path of a filtrate rate since blood protein cannot adhere easily, there is no publication about dialysis engine performance, like the permeability of albumin is low.

[0009] the approach of this invention person drying the humid film which has the specific engine performance, without sinking into low volatility organic liquids, such as a glycerol, and manufacturing the highly efficient blood purification film -- having proposed (patent reference 6) -- when it was made the shape of a thread and dried, it became clear by the core of a thread, and the film of the periphery section that some engine-performance difference arises.

[0010]

[Patent reference 1] JP,6-277470,A [the patent reference 2] JP,11-332980,A [the patent reference 3] JP,8-52331,A [the patent reference 4] JP,8-9668,B [the patent reference 5] JP,6-296686,A [the patent reference 6] The patent No. 3281364 official report [0011]

[Problem(s) to be Solved by the Invention] The technical problem of this invention has very few elution volumes from the film, and they are for adhesion of blood protein and a platelet to offer the approach of manufacturing the small hollow filament-like film of dispersion in engine performance, such as the amount of water penetration, and permeability, especially, in few outstanding manufacture approaches of the hollow filament-like film. Moreover, the technical problem of this invention is related also with offering the module in which dispersion does not have engine performance, such as water permeability and transmission, in a core and the periphery section.

[0012]

[Means for Solving the Problem] There was no desiccation film for blood purification which has the dialysis engine performance dried without using the pit hold-back agent leading to the effluent from a module to this invention person's etc. application invention (patent reference 6) like the above. When the cause was dried without using a pit hold-back agent, the damp or wet condition was becoming completely different film of the low engine performance. Then, this invention person etc. produces beforehand the humid film which has the specific engine performance which is a diameter of an osculum in the amount of high water penetration rather than the target engine performance by application in the first half. There is nothing to the former of manufacturing the film which is made dried and contracting this and has the dialysis engine performance of a target. As a result of advancing research wholeheartedly based on the way of thinking that nobody thought of, there were very few effluents and the approach of obtaining the film which has the dialysis engine performance adhesion of blood protein and a platelet excelled [ engine performance ] in little permselectivity was offered. Then, when research was advanced further, this invention persons discovered that dispersion arose in the amount of water penetration, or penetrable ability by the core of a thread, and the film of the periphery section, when manufacturing the blood purification film by the approach of the patent

reference 6, and the humid film was made into the shape of a thread and it dried. Then, in order to abolish dispersion, as a result of inquiring wholeheartedly, it results that dispersion is suppressed in header this invention with devising a desiccation process.

[0013] Namely, this invention consists of a polysulfone system polymer and a polyvinyl pyrrolidone. The humid film which does not contain the pit maintenance material of a big aperture in the amount of high water penetration is manufactured beforehand. In the approach of manufacturing the dry hollow filament-like film with few effluents which includes the process which makes unnecessary further a part of polyvinyl pyrrolidone in the film in water after shrinking the aperture of this humid film by drying after desolventization It is related with the manufacture approach of the hollow filament-like film characterized by performing the desiccation process of the humid film by microwave exposure.

[0014] When drying in this invention, it is desirable to \*\*\*\* the hollow filament-like film in the shape of a thread, and to pass a dehumidification gas in this thread. It is still more desirable to lessen the difference of the water content of the film in the core and the periphery section of a thread within 10% in this invention at the time of desiccation initiation.

[0015] Furthermore, this invention relates also to the approach of reducing the output of a microwave exposure or changing from microwave exposure desiccation to with a 40-degree-C or more temperature [ temperature 120 degrees C or less ] stoving, when the water content of the thread after desiccation initiation becomes 20 - 70%. It is still more desirable in that case that the difference of the water content of the film in the core and the periphery section of this thread in the time of the water content of the thread after desiccation initiation becoming 20 - 70% is less than 5%. In the above-mentioned approach, a film production undiluted solution consists of a polysulfone system polymer, a polyvinyl pyrrolidone, and a solvent, and it is desirable that the ratio of the polyvinyl pyrrolidone to a polysulfone system polymer is 18 - 27 % of the weight. This invention relates also to the module which consists of hollow filament-like film manufactured as mentioned above again. The hollow filament-like film of this invention is excellent in the hemodialysis engine performance, and is used as hollow filament-like film for hemodialysis. Furthermore, it is useful also as film for other extracorporeal circulation therapies.

[0016]

[Embodiment of the Invention] Below, the configuration of the hollow filament-like film (only henceforth the "film") of this invention is explained. The manufacture approach of this invention manufactures the humid film of a big aperture beforehand in the amount of high water penetration, and has the description to make it dry without infiltrating a pit hold-back agent after desolventization.

[0017] Usually, it is classified into the inorganic substance with which the pit hold-back agent used in case the hollow filament-like film is manufactured is anxious about the toxicity to the organic substance and the body which have viscosity. Since the pit hold-back agent which consists of the organic substance which has viscosity has high viscosity and it is difficult to carry out washing removal completely, it can change with the cause which remains in the film, is made to increase the elution volume from the film, reacts chemically with the pit hold-back agent which remained further, and produces deleterious material. On the other hand, since it remains in a minute amount also in the pit hold-back agent which consists of an inorganic substance, it is apprehensive about the bad influence which it has on a dialysis patient.

[0018] The pit hold-back agent as used in the field of this invention is matter put in the hole part in the film in the manufacture process before drying in order to prevent the degradation at the time of desiccation. It is possible by immersing the humid film in the solution containing a pit hold-back agent to put this hold-back agent in the hole part in the film. If even washing and removal carry out a pit hold-back agent also even for after desiccation, it is possible to hold engine performance, such as the amount of water penetration equivalent to the humid film and rejection, according to the effectiveness of a pit hold-back agent.

[0019] As a pit hold-back agent, ethylene glycol, propylene glycol, A trimethylene glycol, 1, 2-butylene glycol, 1, 3-butylene glycol, 2-butene -1, 4-diol, the 2-methyl -2, 4-PENTA diol, 2-

ethyl -1, 3-hexandiol, a glycerol, tetraethylene glycol, The organic compound and calcium chlorides of a polyethylene glycol 200, a polyethylene glycol 300, and polyethylene-glycol 400 grade, such as a glycol system or a glycerol system compound, and a sucrose fatty acid ester, The mineral salt of a sodium carbonate, sodium acetate, magnesium sulfate, a sodium sulfate, a zinc chloride, etc. can be mentioned.

[0020] Moreover, in this invention, the amounts of water penetration are 100mL(s) / (m2 and hr-mmHg) above in the amount of high water penetration, and the humid film of a big aperture means the humid film which the transmission of the polyvinyl pyrrolidone of weight average molecular weight 40,000 exceeds 75%, and has the engine performance whose transmission of the albumin in a cow plasma system is 0.3% or more.

[0021] The permeability of cow plasma albumin can be measured by the following approaches. First, 100 hollow filament-like film with a die length of 20cm is bundled, and a small module is produced. The heparinize cow plasma (heparin 5000 IU/L (liter), protein concentration 6.0 g/dL (deciliter)) warmed to this module at 37 degrees C is passed with the linear velocity of 1.0cm/second to a film internal-surface side, a module enters, and an ultrafiltration is performed for 30 minutes in mean-pressure 50mmHg of \*\* and \*\*\*\*. It computes permeability by measuring measurement of the concentration of the obtained filtrate and former liquid on the wavelength of 280nm with an ultraviolet spectroscopy photometer, and substituting it for the following formula (1).

Permeability (%) = (absorbance of filtrate) x 100 / (absorbance of former liquid) (1)

[0022] The transmission of a polyvinyl pyrrolidone is called for by performing the same actuation as measurement of the transmission of cow plasma albumin except having used the water solution to filter as the phosphoric-acid buffer (0.15-mol [ // l. ], pH7.4) water solution of 3% of the weight of a polyvinyl pyrrolidone (BASF A.G. make K30, weight average molecular weight 40,000), and the module having entered and having set the mean pressure of \*\* and \*\*\*\* to 200mmHg(s).

[0023] After the humid film of a big aperture making a polysulfone system polymer (only henceforth a "polymer"), a polyvinyl pyrrolidone, and the film production undiluted solution that consists of a solvent breathe out from a double annular nozzle with internal liquid in the amount of high water penetration and passing an air gap, in the manufacture approach made to solidify by the coagulation bath, it can manufacture by using the water solution of the solvent of a polymer for internal liquid.

[0024] Although internal liquid makes a membranous centrum and a membranous internal surface form, it turns out that the aperture of an internal surface becomes large in proportion to the solvent concentration in internal liquid. In this invention, since the permeable membrane of the engine performance of a target is obtained by carrying out drying shrinkage of the humid film, compared with the time of manufacturing the humid film which has the target solvent concentration in internal liquid dialysis-engine performance, it is necessary to make it high concentration.

[0025] What has the repeat unit shown by the following formula (2) or the formula (3) as a polysulfone system polymer used by this invention is mentioned. In addition, Ar in a formula shows the phenyl group of two permutations in the para position, and limits neither about polymerization degree nor especially molecular weight.

-O-Ar-C(CH<sub>3</sub>)<sub>2</sub>-Ar-O-Ar-SO<sub>2</sub>-Ar- (2)

-O-Ar-SO<sub>2</sub>-Ar- (3)

[0026] Since the hydrophilization effectiveness to the film is as high as the thing of the amount of macromolecules and little and as sufficient effectiveness as the thing of the amount of macromolecules can demonstrate a polyvinyl pyrrolidone, in this invention, a with a weight average molecular weight of 900,000 or more polyvinyl pyrrolidone is used. Although it is necessary to make a lot of polyvinyl pyrrolidones remain in the film in order to give the hydrophilization effectiveness to the film using the polyvinyl pyrrolidone which has weight average molecular weight smaller than 900,000 for this reason, the effluent from the film will increase. Moreover, in order to lower an effluent conversely, when the amount of survival in the

inside of the film of the polyvinyl pyrrolidone of weight average molecular weight smaller than 900,000 was lessened, the hydrophilization effectiveness becomes inadequate and hemodialysis is performed as a result, the fall of filtration velocity with time is caused and sufficient effectiveness cannot be demonstrated.

[0027] Moreover, both the solvents used for the dissolution of a polysulfone system polymer and a polyvinyl pyrrolidone dissolve both these, and are a N-methyl-2-pyrrolidone, N,N-dimethylformamide, N,N-dimethylacetamide, etc.

[0028] Especially if the polymer concentration in a film production undiluted solution is the range of concentration where the film which could produce the film and was obtained has the engine performance as film, it will not be restricted, but it is 10 - 30 % of the weight preferably five to 35% of the weight. In order to attain permeable high ability, the lower one of polymer concentration is good, and its 10 - 25 % of the weight is desirable.

[0029] A still more important thing is the addition of a polyvinyl pyrrolidone, and it is 20 - 27 % of the weight still more preferably ten to 27% of the weight preferably 27 or less % of the weight of mixing ratio GA of a polyvinyl pyrrolidone to a polymer. It is difficult to be in the inclination whose elution volume increases, when the mixing ratio of the polyvinyl pyrrolidone to a polymer exceeds 27 % of the weight, and to obtain the film of sponge structure, since the viscosity of a film production undiluted solution is low at less than 10 % of the weight. Moreover, what is necessary is it to be also possible for to add the 4th component, such as water and a poor solvent, in order to control undiluted solution viscosity and a dissolution condition, and for combination just to perform the class and an addition at any time.

[0030] Water is desirable although the liquid which does not dissolve polymers, such as aliphatic hydrocarbon, such as alcohols; ether;n-hexanes, such as a water; methanol and ethanol, and n-heptane, for example is used as a coagulation bath. Moreover, it is also possible to control a coagulation rate by adding a little the solvent which dissolves a polymer in a coagulation bath.

[0031] -30-90 degrees C of 0-90 degrees C of temperature of a coagulation bath are 0-80 degrees C still more preferably preferably. The temperature of a coagulation bath exceeds 90 degrees C, or the surface state of the hollow filament-like film in a coagulation bath cannot be easily stabilized as it is less than -30 degrees C.

[0032] Desiccation after desolventization washing is performed by irradiating microwave at the thread which is fully carrying out humidity with the gestalt (it is only henceforth called a "thread") of the thread which bundled several hollow filament-like many film.

[0033] However, since it is suitable for drying the thread of low water content to homogeneity more, in order to prevent deformation and melting of the film by fault heating, when the average water content of a thread becomes 50 - 70% more preferably 20 to 70%, it is desirable [ a microwave exposure ] to reduce the output of a microwave exposure.

[0034] Furthermore, in order that it may suppress dispersion in the engine performance that the difference of the water content of the film in the core and the periphery section of this thread in the time of the average water content of a thread becoming 50 - 70% preferably 20 to 70% is less than 5%, it is desirable. It is possible at the time of desiccation to make the difference of the water content of the film in the core and the periphery section of a thread less than 5% by ventilating in a thread. Here, the core of a thread means one sixth of the range of a diameter from the central point in the circle configuration cross section of a thread. Moreover, the periphery section of a thread means the range of 1/6 from a periphery in the circle configuration cross section of a thread. [0035] Moreover, since it is the same, it is desirable also about the thread at the time of desiccation initiation that the difference of the water content of the film in the core and the periphery section of a thread is less than 10%. If the thread after desolventization is left, since a difference will arise in the water content of the core of a thread, and the periphery section, it is possible by immersing a thread underwater again, just before going into a desiccation process to make the difference of the water content of a thread core and the periphery section less than 10%. Here, water content means what is calculated by count by (4) types from the weight (A (g)) of the thread before desiccation (or film), and the weight (B (g)) of a desiccation thread (or film).



Water content (%) =  $(A-B) \times 100 / B$  (4)

[0036] Furthermore, in order to abolish the difference of the rate of drying of the core of a thread, and the periphery section, it is desirable to ventilate in a thread the dehumidification gas of the temperature which does not exceed 40 degrees C. It means passing a wind between hollow filament-like film as ventilating in a thread. In this invention, ventilating a with a 40-degree-C or more temperature [ temperature 120 degrees C or less ] dehumidification gas in a thread means performing stoving to a thread at the same time it ventilates in a thread.

[0037] Although the high thing of the output of microwave is desirable, an optimum value changes with amounts of the film to dry. Moreover, although the approach of performing two-step desiccation changed from a microwave exposure to with a 40-degree-C or more temperature [ temperature 120 degrees C or less ] ventilation desiccation also takes the drying time rather than a microwave exposure when the water content of a thread becomes 50 - 70% preferably 20 to 70%, it is possible to dry a thread to homogeneity. Also in the two-step drying method, it is effective in suppressing dispersion in the engine performance that the difference of the water content of the film in the core and the periphery section of this thread in the time of the water content of a thread becoming 50 - 70% preferably 20 to 70% is less than 5%.

[0038] It is desirable still more desirable that it is [ 40 degrees-C or more ] 120 degrees C or less, and the temperature of stoving is 100 degrees C or less. If it exceeds 120 degrees C, in order that a polyvinyl pyrrolidone may denaturalize and decompose, it is not desirable from the elution volume from the desiccation film obtained even if it did not use a pit hold-back agent increasing. Moreover, since the drying time starts too much at less than 40 degrees C, it is not desirable.

[0039] Since a part of PVP in the film can be insolubilized in water by irradiating radiations, such as an electron ray and a gamma ray, at the film after desiccation, it is possible to reduce the elution volume from the film more. Whichever after a modularization of the exposure of a radiation is sufficient as a modularization front stirrup. Moreover, if all PVP in the film is insolubilized, while an elution volume can be reduced, it is not desirable from a leuco PENIA symptom being observed at the time of dialysis.

[0040] With PVP insoluble in the water as used in the field of this invention, the meltable amount of PVP is deducted from the total amount of PVP in the film in water. The total amount of PVP in the film is easily computable with the elemental analysis of nitrogen and sulfur. Moreover, the amount of PVP meltable in water can be calculated by the following approaches. After dissolving the film completely by the N-methyl-2-pyrrolidone, water is added in the obtained polymer solution and a polysulfone system polymer is settled completely. After putting this polymer solution furthermore, the quantum of meltable PVP can be carried out to water by carrying out the quantum of the amount of PVP in a supernatant with liquid chromatography.

[0041] The film which was characterized by the manufacture approach of this invention drying the humid film which does not contain a pit hold-back agent by microwave exposure, and was obtained using this manufacture approach it is the desiccation film which does not contain a pit hold-back agent. The permeability of the polyvinyl pyrrolidone of 10-1,000mL/(m2 and hr-mmHg) and weight average molecular weight 40,000 at 75% or less [ the amount of water penetration of pure water ] And the transmission of the albumin in a cow plasma system is less than 0.3%, and it is the hollow filament-like film characterized by the variation in each engine performance being still smaller. Although the beta 2-microglobulin (molecular weight: 11,800) made into the causative agent for the improvement of dialysis amyloid condition of disease is made to fully penetrate in the latest hemodialysis therapy, the film which has the fractionation nature which does not make most albumin (molecular weight: 67,000) penetrate is called for, and the permeability of albumin [ in / in the film of this invention / a cow plasma system ] is 0.3% or less. Since it means losing greatly albumin effective in the inside of the body, it is not desirable as permeable membrane that the transmission of albumin exceeds 0.3%.

[0042] Moreover, the linear correlation which the amount of water penetration of pure water shows in the following formula (5) at the transmission (A (%)) of a polyvinyl pyrrolidone and the path clearance (B (a part for mL/)) of beta 2-microglobulin in the film of 10mL(s) / (m2 and hr-

mmHg) more than exists. Although it is required for path clearance evaluation to fabricate and process the module of the dialysis specification which has the effective film surface product of 2 1.5m, it is possible for it to be measurable in simple and to guess path clearance easily by this evaluation approach.

$B(\text{part for mL}) = 0.636A + 29.99 \quad (5)$

Here, in accordance with the performance-evaluation criteria of Japanese Society for Artificial Organs, dialysis measurement of the path clearance of beta 2-microglobulin is carried out at the module of the effective film surface product of 2 under a part (film internal-surface side) for blood flow rate 200mL/, and the conditions for dialysing fluid flow rate 500mL/(film outside-surface side) 1.5m.

[0043] Although, as for the path clearance of beta 2-microglobulin, various things are demanded according to a dialysis patient's physical strength, or the percentage of completion of condition of disease and condition of disease, if the transmission of a polyvinyl pyrrolidone exceeds 75%, since the transmission of albumin will exceed 0.3%, the transmission of a polyvinyl pyrrolidone needs to be 75% or less.

[0044] Moreover, since the pit hold-back agent is not being used for the film made by the manufacture approach of this invention by the production process, the effluent of the pit hold-back agent origin does not exist. Therefore, the absorbance of the effluent test fluid of the film of this invention is less than 0.04, and does not contain a pit hold-back agent in this test fluid. With effluent test fluid, it adjusts here based on hemodialysis apparatus acknowledgement criteria, and after putting 1.5g of desiccation hollow filament-like film cut to 2cm, and distilled-water-for-injection 150mL into the glassware which suits the alkali dissolution test of the glassware trial for injection of a Japanese pharmacopoeia, warming at 70±5 degrees C for 1 hour and removing the film after cooling, what added distilled water and was set to 150mL(s) is meant. An absorbance is measured with an ultraviolet absorption spectrum on the wavelength which shows the maximum absorption wavelength in 220-350nm. Although making an absorbance or less into 0.1 is defined on hemodialysis apparatus acknowledgement criteria, since the film of this invention does not hold a pit hold-back agent, it can attain less than 0.04. Moreover, about the existence of a pit hold-back agent, it is detectable by measuring the thing which condensed or removed [ moisture ] this test fluid by well-known approaches, such as a gas chromatography, liquid chromatography, differential refractive media, an ultraviolet spectroscopy photometer, an infrared absorptiometry, nuclear-magnetic-resonance spectroscopy, and elemental analysis. Moreover, it is detectable also about whether a pit hold-back agent is included in the film with these measuring methods.

[0045] The film made by the manufacture approach of this invention consists of a polysulfone system polymer and a polyvinyl pyrrolidone, and the concentration of the polyvinyl pyrrolidone in a film internal surface is 30 - 45 % of the weight. By the polysulfone system film which is the hydrophilic property of the film internal surface which blood touches, and contains a polyvinyl pyrrolidone (only henceforth "PVP"), the PVP concentration of a film internal surface is important for a factor important for membranous haemocompatibility. When the PVP concentration of a film internal surface is too low, a film internal surface shows hydrophobicity, plasma protein tends to adsorb, and the coagulation of blood also tends to take place. That is, it becomes membranous poor haemocompatibility. Conversely, if the PVP concentration of a film internal surface is too high, the elution volume to the blood system of PVP will increase, and the result which is not desirable will be given for the purpose and application of this invention. Therefore, the concentration of PVP of the film internal surface in this invention is 30 - 40% of range, and is 33 - 40% preferably.

[0046] The PVP concentration of a film internal surface is determined by the X ray photon spectrum (X-ray Photoelectron spectroscopy, henceforth, XPS). That is, after measurement of XPS of a film internal surface arranges a sample in on a double-sided tape, a cutter cuts it open to fiber shaft orientations, and after extending so that the membranous inside may become a table, it is measured by the usual approach. That is, C1s and O1s, the concentration for which it asked using the relative sensitivity coefficient of equipment attachment from the surface

concentration (nitrogen atom concentration) of nitrogen and sulphuric surface concentration (sulfur atom concentration) is said from the integrated intensity of N1s and an S2p spectrum, and when a polysulfone system polymer is the structure of (2) types, it can ask by count by (6) types.

PVP concentration (% of the weight) =  $C1M1 \times 100 / (C1M1 + C2M2)$  (6)

It is here and is C1:nitrogen atom concentration (%).

C2: Sulfur atom concentration (%)

M1 : P Molecular weight of the repeat unit of VP (111)

M2: Molecular weight of the repeat unit of a polysulfone system polymer (442)

[0047]

[Example] Although the example of this invention is shown below, this invention is not limited to this.

(Measurement of the amount of platelet adhesion) The following operating procedure performed measurement of the amount of platelet adhesion to the film. Bundle 100 hollow filament-like film with a die length of 15cm, produce a small module, and this module is made to pass heparinize Homo sapiens fresh blood for 15 minutes with the linear velocity of 1.0cm/second, and the physiological saline was continuously passed for 1 minute. Next, it computed as LDH activity of per a film surface product (internal-surface conversion) by carrying out the quantum of the lactate dehydrogenase (henceforth "LDH") emitted from the platelet which carried out beating of the hollow filament-like film to 5mm spacing extent, carried out ultrasonic irradiation in the physiological saline which contains the polyethylene-glycol alkylphenyl ether (Wako Pure Chem trade name triton X-100) 0.5%, and adhered to the film front face. Measurement of enzyme activity used the LDH mono-test kit (Boehringer Mannheim and made in Yamanouchi). In addition, it compared with a specimen and coincidence using the film (what was obtained by being immersed in ethanol for one day after the film of the example 1 in front of gamma irradiation was immersed in the sodium hypochlorite with an available chlorine concentration of 1,500 ppm for two days) which does not contain PVP as positive control.

[0048] (Plasma protein amount of adsorption) Except having carried out ultrafiltration time amount in 240 minutes, after the plasma protein amount of adsorption to the film performed the same actuation as the transmissometry of albumin, the physiological saline washed it for 1 minute. Next, it computed as the protein amount of adsorption per film weight by carrying out beating of the hollow filament-like film to 5mm spacing extent, and carrying out the quantum of the plasma protein stirred and extracted in the physiological saline which contains sodium lauryl sulfate 1.0%. Protein concentration used BCA protein assay (made in Pierce). In addition, it compared with a specimen and coincidence using the film (what was obtained by being immersed in ethanol for one day after the film of the example 1 in front of gamma irradiation was immersed in the sodium hypochlorite with an available chlorine concentration of 1,500 ppm for two days) which does not contain PVP as positive control.

[0049]

[Example 1] (Film production and removal of a residual solvent) It dissolved in 77.7 % of the weight of N,N-dimethylacetamide, and 18.0 % of the weight (product made from Amoco Engineering Polymers P-1700) of polysulfones and 4.3 % of the weight (BASF A.G. make K90, weight average molecular weight 1,200,000) of polyvinyl pyrrolidones were used as the uniform solution. Here, the mixing ratio of the polyvinyl pyrrolidone to the polysulfone in a film production undiluted solution was 23.9 % of the weight. This film production undiluted solution was kept at 60 degrees C, and it was immersed to the coagulation bath which is made to breathe out from a spinning port (double annular nozzle 0.1mm - 0.2 mm to 0.3 mm), is made to pass a 0.96m air gap, and consists of 75-degree C water with the internal liquid which consists of a mixed solution of 30 % of the weight of N,N-dimethylacetamide, and 70 % of the weight of water. At this time, from a spinning port to the coagulation bath was surrounded by the cylinder-like cylinder, the humidity in a cylinder was controlled and temperature was controlled for the nitrogen gas which contained the steam in the cylinder at 51 degrees C 54.5% with the sink. Spinning speed was fixed to a part for 80m/. Here, the ratio of the air gap to spinning

speed was 0.012m/(a part for m/). The residual solvent in the film was removed after cutting the rolled-round thread by washing a 80-degree C hot water shower over 2 hours from the cutting plane upper part of a bundle (die length of 300mm, 9200 film numbers).

[0050] (Desiccation of the humid film and insolubilization processing of PVP) The microwave exposure (output of 30kW) of the 30 threads after the above-mentioned residual solvent removal (the difference of the water content of the film [ in / water content / of the film of 300% and a thread core / water content / in the water content of the film of 300% and the thread periphery section / the core and the periphery section of 300% and a thread ] is 0%) was carried out for 21 minutes. At this time, the water content of a thread was 65% (the difference of the water content of the film [ in / water content / of the film of a thread core / in the water content of the film of 65% and the thread periphery section / the core and the periphery section of 65% and a thread ] is 0%). Then, water content obtained less than 1% of desiccation film (thread) by dropping an output and carrying out a microwave exposure (output of 21kW) for 4 minutes. Moreover, dehumidification air (10% or less of humidity) was ventilated from the lower part of each thread from the lower part of a thread to the upper part at the 8m [/second] wind speed between the time of desiccation initiation, and the time of desiccation termination. At this time, the 1m [/second] wind speed was measured by the thread average from the upper part of a thread at the time of desiccation initiation. Furthermore, a part of PVP in the film was insolubilized by irradiating the gamma ray of 25kG(ies) at the obtained desiccation film (thread).

[0051] (Performance-evaluation result) The engine performance of this film is shown in Table 1. The engine performance shows the average of the result measured 10 times. When this film was used as the module of 2 the effective filtration area of 1.5m and path clearance of beta 2-microglobulin was surveyed, it turned out that it is by part for 32mL/, and it became clear that it is equivalent to a part for path clearance 32.5mL/computed by having substituted it for the formula (6). Furthermore, when this module performed transit measurement of a urea and vitamin B12, the path clearance and the permeability of a urea were part 83% for 185mL(s)/, respectively. Moreover, about vitamin B12, it was part 48% for 95mL(s)/similarly. Measurement is [0042]. It carried out by the same approach. Moreover, 62% of the total amount of PVP in the film was insoluble in water. As a result of carrying out a membranous eluting material test, the absorbance of effluent test fluid was 0.04 or less. Moreover, since the pit hold-back agent was not used, in effluent test fluid, the pit hold-back agent was contained and was not. Furthermore, as for this film, compared with the positive control film, the amount of platelet adhesion became low (positive control film 43.4 Unit/m<sup>2</sup>) clear [ that the amount of adhesion of plasma protein is also low ] (positive control film 62.5 mg/g).

[0052] It became clear that this film has very few elution volumes from the film, and there is little adhesion of blood protein and a platelet from the engine performance mentioned above. Moreover, since the transmission of albumin was excellent also in the path clearance of beta 2-microglobulin few, it turned out that it is the film excellent also in the dialysis engine performance. Furthermore, since there were few differences of the engine performance of the film in the core and the periphery section of a thread compared with the old desiccation approach (example 1 of a comparison), dispersion in the engine performance became clear [ few things ].

[0053]

[Example 2] The same actuation as an example 1 was performed except having made the polyvinyl pyrrolidone in a film production undiluted solution, and having made N,N-dimethylacetamide into 78 % of the weight 4% of the weight. The mixing ratio of the polyvinyl pyrrolidone to the polysulfone in the film production undiluted solution at this time was 22.2 % of the weight. The engine performance of this film is shown in Table 1. It became clear that this film has very few elution volumes from the film, and there is little adhesion of blood protein and a platelet. Moreover, there was little transmission of albumin, and since excelling also in the path clearance of beta 2-microglobulin was suggested, it turned out that it is the film excellent also in the dialysis engine performance. Furthermore, since there were few differences of the engine performance of the film in the core and the periphery section of a thread compared with

the old desiccation approach (example 1 of a comparison), dispersion in the engine performance became clear [ few things ].

[0054]

[Example 3] The same actuation as an example 1 was performed except having made the polyvinyl pyrrolidone in a film production undiluted solution, and having made N,N-dimethylacetamide into 77.2 % of the weight 4.8% of the weight. The mixing ratio of the polyvinyl pyrrolidone to the polysulfone in the film production undiluted solution at this time was 26.7 % of the weight. The engine performance of this film is shown in Table 1. It became clear that this film has very few elution volumes from the film, and there is little adhesion of blood protein and a platelet. Moreover, there was little transmission of albumin, and since excelling also in the path clearance of beta 2-microglobulin was suggested, it turned out that it is the film excellent also in the dialysis engine performance. Furthermore, since there were few differences of the engine performance of the film in the core and the periphery section of a thread compared with the old desiccation approach (example 1 of a comparison), dispersion in the engine performance became clear [ few things ].

[0055]

[Example 4] The same actuation as an example 3 was performed except having used the mixing solution which turns into internal liquid from 52 % of the weight of N,N-dimethylacetamide, and 48 % of the weight of water. The engine performance of this film is shown in Table 2. It became clear that this film has very few elution volumes from the film, and there is little adhesion of blood protein and a platelet. Moreover, there was little transmission of albumin, and since excelling also in the path clearance of beta 2-microglobulin was suggested, it turned out that it is the film excellent also in the dialysis engine performance. Furthermore, since there were few differences of the engine performance of the film in the core and the periphery section of a thread compared with the old desiccation approach (example 1 of a comparison), dispersion in the engine performance became clear [ few things ].

[0056]

[Example 5] The thread after residual solvent removal (the water content of the film of a thread core 300% 300%) [ water content ] After the difference of the water content of the film [ in / in the water content of the film of the thread periphery section / the core and the periphery section of a thread ] carries out the microwave exposure (output of 30kW) of 30 for 21 minutes 0% 300%. The water content of a thread is 65% (the water content of the film of the thread periphery section 65% 65%). [ the water content of the film of a thread core ] After checking that the difference of the water content of the film in the core and the periphery section of a thread is 0%, except that stoving was carried out and water content obtained less than 1% of thread by putting into the dryer (3m [ /second ] circulation wind speed in a dryer) set as 87 degrees C for 3 hours, the same actuation as an example 1 was performed. The engine performance of this film is shown in Table 2. It became clear that this film has very few elution volumes from the film, and there is little adhesion of blood protein and a platelet. Moreover, there was little transmission of albumin, and since excelling also in the path clearance of beta 2-microglobulin was suggested, it turned out that it is the film excellent also in the dialysis engine performance. Furthermore, since there were few differences of the engine performance of the film in the core and the periphery section of a thread compared with the old desiccation approach (example 1 of a comparison), dispersion in the engine performance became clear [ few things ].

[0057]

[The example 1 of a comparison] The thread after residual solvent removal (the water content of the film of a thread core 300% 300%) [ water content ] The difference of the water content of the film [ in / in the water content of the film of the thread periphery section / the core and the periphery section of a thread ] 300% 30 0% Except that stoving was carried out and water content obtained less than 1% of thread by putting into the dryer (3m [ /second ] circulation wind speed in a dryer) set as 87 degrees C for 7 hours, the same actuation as an example 1 was performed. This result is shown in Table 2. A difference is in the engine performance of the

film in the core and the periphery section of a thread in the permeability of water penetration  
 \*\*\*\* PVP, and it became clear that there is dispersion in the engine performance within a thread as a result.

[0058]

[The example 2 of a comparison] The same actuation as an example 1 was performed except there being nothing gamma ray Teru putting. This result is shown in Table 3. It became clear that the absorbance of elution test liquid exceeds 0.04 for the elution of PVP.

[0059]

[The example 3 of a comparison] The same actuation as an example 1 was performed except having made the polyvinyl pyrrolidone in a film production undiluted solution, and having made N,N-dimethylacetamide into 77.0 % of the weight 5.0% of the weight. The mixing ratio of the polyvinyl pyrrolidone to the polysulfone in the film production undiluted solution at this time was 27.8 % of the weight. The engine performance of this film is shown in Table 3. Since the mixing ratio of the polyvinyl pyrrolidone to the polysulfone in a film production undiluted solution is over 27 % of the weight, an elution volume and film internal-surface PVP concentration are increasing. [0060]

[The example 4 of a comparison] The same actuation as an example 1 was performed except having made the polyvinyl pyrrolidone in a film production undiluted solution, and having made N,N-dimethylacetamide into 78.4 % of the weight 3.6% of the weight. The mixing ratio of the polyvinyl pyrrolidone to the polysulfone in the film production undiluted solution at this time was 20.0 % of the weight. The engine performance of this film is shown in Table 3. It became clear that the amount of PVP of a film internal surface is less than 30%.

[0061]

[The example 5 of a comparison] The same actuation as an example 3 was performed except having used the mixing solution which turns into internal liquid from 60 % of the weight of N,N-dimethylacetamide, and 40 % of the weight of water. The engine performance of this film is shown in Table 3. This film was engine performance for which the permeability of albumin is over 0.3%, and the permeability of PVP also exceeds 75%.

[0062]

[The example 6 of a comparison] The same actuation as an example 1 was performed except having used the mixing solution which turns into internal liquid from 10 % of the weight of N,N-dimethylacetamide, and 90 % of the weight of water. The engine performance of this film is shown in Table 3. The amount of water penetration of pure water was the engine performance which is less than 10mL(s)/(m2 and hr-mmHg).

[0063]

[The example 7 of a comparison] The same actuation as an example 1 was performed except having made drying temperature into 170 degrees C. The engine performance of this film is shown in Table 3. All PVP in the film of this film was insoluble in water. When this film was used as the module of 2 the effective filtration area of 1.5m and clinical blood evaluation was carried out in accordance with the performance-evaluation criteria of Japanese Society for Artificial Organs under a part (film internal-surface side) for blood flow rate 200mL/, and the conditions for dialysing fluid flow rate 500mL/(film outside-surface side), the leuco PENIA symptom that a dialysis patient's white blood cell count fell temporarily was observed.

[0064]

[Table 1]

	実施例 1		実施例 2		実施例 3	
	系東中心部	系東外周部	系東中心部	系東外周部	系東中心部	系東外周部
膜内径( $\mu\text{m}$ )	195	195	201	201	190	190
膜外径( $\mu\text{m}$ )	280	280	288	288	282	282
透水量( $\text{mL}/(\text{m}^2 \cdot \text{hr} \cdot \text{mmHg})$ )	20	20	19	18	25	25
アルブミンの透過率 (%)	0.01 以下	0.01 以下	0.01 以下	0.01 以下	0.01 以下	0.01 以下
PVP の透過率 (%)	4	4	4	4	5	5
膜内表面 PVP 濃度(重量%)	35	35	30	30	44	44
水に不溶である PVP の有無	有り	有り	有り	有り	有り	有り
溶出物試験液の吸光度	0.022	0.022	0.020	0.020	0.035	0.035
溶出物試験液中の膜孔保持剤の有無	無し	無し	無し	無し	無し	無し
血小板粘着量 ( $\text{LDH-Unit}/\text{m}^2$ )	15.5	15.5	17.5	17.5	4.2	4.2
血漿タンパク質吸着量 ( $\text{mg}/\text{g}$ )	2.1	2.1	5.5	5.5	1.8	1.8
乾燥前湿潤膜の透水量( $\text{mL}/(\text{m}^2 \cdot \text{hr} \cdot \text{mmHg})$ )	190	190	170	170	260	260
乾燥前湿潤膜のアルブミンの透過率 (%)	0.32	0.32	0.34	0.34	0.35	0.35
乾燥前湿潤膜の PVP の透過率 (%)	77	77	84	84	84	84

[0065]

[Table 2]

	実施例 4		実施例 5		比較例 1	
	系東中心部	系東外周部	系東中心部	系東外周部	系東中心部	系東外周部
膜内径( $\mu\text{m}$ )	194	194	196	195	195	195
膜外径( $\mu\text{m}$ )	284	284	280	280	281	280
透水量( $\text{mL}/(\text{m}^2 \cdot \text{hr} \cdot \text{mmHg})$ )	390	390	22	20	28	20
アルブミンの透過率 (%)	0.25	0.25	0.01 以下	0.01 以下	0.01 以下	0.01 以下
PVPの透過率 (%)	72	72	4	4	8	4
膜内表面 PVP 濃度(重量%)	36	36	35	35	35	35
水に不溶である PVPの有無	有り	有り	有り	有り	有り	有り
溶出物試験液の吸光度	0.023	0.023	0.022	0.022	0.022	0.022
溶出物試験液中の膜孔保持剤の有無	無し	無し	無し	無し	無し	無し
血小板粘着量 ( $\text{LDH} \cdot \text{Unit}/\text{m}^2$ )	13.8	13.8	15.6	15.5	15.6	15.5
血漿タンパク質吸着量 ( $\text{mg/g}$ )	2.0	2.0	2.1	2.1	2.1	2.1
乾燥前湿潤膜の透水量( $\text{mL}/(\text{m}^2 \cdot \text{hr} \cdot \text{mmHg})$ )	3100	3100	190	190	190	190
乾燥前湿潤膜のアルブミンの透過率 (%)	0.51	0.51	0.32	0.32	0.32	0.32
乾燥前湿潤膜の PVP の透過率 (%)	99	99	77	77	77	77

[0066]

[Table 3]



	比較例 2	比較例 3	比較例 4	比較例 5	比較例 6	比較例 7
	糸束外周部	糸束外周部	糸束外周部	糸束外周部	糸束外周部	糸束外周部
膜内径( $\mu\text{m}$ )	195	200	199	196	200	191
膜外径( $\mu\text{m}$ )	290	298	290	297	291	276
透水量( $\text{mL}/(\text{m}^2 \cdot \text{hr} \cdot \text{mmHg})$ )	20	35	15	970	8	15
アルブミンの透過率(%)	0.01 以下	0.01 以下	0.01 以下	0.37	0.01 以下	0.01 以下
PVPの透過率(%)	4	5	4	79	0	4
膜内表面 PVP 濃度(重量%)	35	47	28	33	34	36
水に不溶である PVP の有無	無し	有り	有り	有り	有り	有り
溶出物試験液の吸光度	0.044	0.040	0.018	0.021	0.020	0.021
溶出物試験液中の膜孔保持剤の有無	無し	無し	無し	無し	無し	無し
血小板粘着量(LDH-Unit/ $\text{m}^2$ )	15.5	3.8	19.6	15.0	15.1	16.8
血漿タンパク質吸着量( $\text{mg/g}$ )	2.1	1.1	5.9	2.8	2.1	3.0
乾燥前湿潤膜の透水量( $\text{mL}/(\text{m}^2 \cdot \text{hr} \cdot \text{mmHg})$ )	190	310	130	8600	76	190
乾燥前湿潤膜のアルブミンの透過率(%)	0.32	0.38	0.31	0.62	0.18	0.32
乾燥前湿潤膜の PVP の透過率(%)	77	85	76	100	52	77

[0067]

[Effect of the Invention] The film of this invention has very few elution volumes from the film, and since it has the outstanding dialysis engine performance with little adhesion of blood protein and a platelet, it can be used for a physic application, a medical-application way, and a general industrial use way.

[Translation done.]

(19) 日本国特許庁 (J P)

## (12) 公開特許公報 (A)

(11) 特許出願公開番号

特開2003-175320

(P2003-175320A)

(43) 公開日 平成15年6月24日 (2003.6.24)

(51) Int. Cl. <sup>7</sup> B 0 1 D 69/08 61/24 63/02 67/00	識別記号    5 0 0	F I B 0 1 D 69/08 61/24 63/02 67/00	データベース <sup>*</sup> (参考) 4 D 0 0 6
審査請求 未請求 請求項の数 9 O L (全 11 頁) 最終頁に続く			
(21) 出願番号  (22) 出願日  (31) 優先権主張番号 (32) 優先日 (33) 優先権主張国	特願2002-292729 (P2002-292729)  平成14年10月4日 (2002.10.4)  特願2001-309673 (P2001-309673) 平成13年10月5日 (2001.10.5) 日本 (J P)	(71) 出願人 旭メディカル株式会社 東京都千代田区神田美土代町9番地1 (72) 発明者 大石 輝彦 宮崎県延岡市旭町4丁目3400番地1 旭メ ディカル株式会社内 (72) 発明者 緒方 益次郎 宮崎県延岡市旭町4丁目3400番地1 旭メ ディカル株式会社内 (74) 代理人 100090941 弁理士 藤野 清也 (外2名)	最終頁に続く

(54) 【発明の名称】 中空糸状膜の製造方法

## (57) 【要約】

【課題】 膜からの溶出量が極めて少なく、血液タンパク質や血小板の付着が少ない優れた透析性能を有する乾燥膜の製造方法において、特に透水量及び透過率等の性能のばらつきの小さな中空糸状膜を得る方法を提供すること。

【解決手段】 ポリスルホン系ポリマーとポリビニルピロリドンからなる高透水量で大きな孔径の膜孔保持材を含まない湿潤膜をあらかじめ製造しておき、脱溶剤後乾燥することにより該湿潤膜の孔径を収縮させた後、さらに膜中のポリビニルピロリドンの一部を水に不溶化する工程を含む、溶出物の少ない乾燥した中空糸状膜を製造する方法であって、湿潤膜の乾燥工程をマイクロ波照射によって行うことを特徴とする中空糸状膜の製造方法、及び該方法によって得られた中空糸状膜からなるモジュール。

## 【特許請求の範囲】

【請求項1】 ポリスルホン系ポリマー及びポリビニルピロリドンからなる、高透水量で大きな孔径の膜孔保持材を含まない湿潤膜をあらかじめ製造しておき、脱溶剤後乾燥することにより該湿潤膜の孔径を収縮させた後、さらに膜中のポリビニルピロリドンの一部を水に不溶化する工程を含む、溶出物の少ない乾燥した中空糸状膜を製造する方法であって、湿潤膜の乾燥工程をマイクロ波照射によって行うことを特徴とする中空糸状膜の製造方法。

【請求項2】 乾燥時に中空糸状膜が糸束状に製束されており、該糸束内に除湿気体を通風することを特徴とする請求項1に記載の製造方法。

【請求項3】 乾燥開始時の糸束の中心部と外周部における膜の含水率の差が10%以内であることを特徴とする請求項2に記載の製造方法。

【請求項4】 乾燥開始後、糸束の平均含水率が20~70%になる時点で、マイクロ波照射の出力を低下させることを特徴とする請求項2または3に記載の製造方法。

【請求項5】 乾燥開始後、糸束の平均含水率が20~70%になる時点で、マイクロ波照射乾燥から40℃以上120℃以下の温度の加熱乾燥に切り替えることを特徴とする請求項2または3に記載の製造方法。

【請求項6】 乾燥開始後の糸束の平均含水率が20~70%になる時点で該糸束の中心部と外周部における膜の含水率の差が5%以内であることを特徴とする請求項4または5に記載の製造方法。

【請求項7】 製膜原液が、ポリスルホン系ポリマー、ポリビニルピロリドン、及び溶剤からなり、ポリスルホン系ポリマーに対するポリビニルピロリドンの比率が18~27重量%であることを特徴とする請求項1~6のいずれかに記載の製造方法。

【請求項8】 請求項1~7のいずれかに記載の方法によって製造される中空糸状膜からなるモジュール。

【請求項9】 血液透析用である請求項8に記載のモジュール。

## 【発明の詳細な説明】

## 【0001】

【発明の属する技術分野】 本発明は、膜からの溶出量が極めて少なく、血液タンパク質や血小板の付着が少ない優れた透析性能を有する高性能中空糸膜の製造方法において、特に透水量及び透過率等の性能のばらつきの小さな中空糸膜を製造する方法に関する。また、本発明は、そのように製造された中空糸膜からなるモジュールにも関する。

## 【0002】

【従来の技術】 近年、選択的な透過性を有する膜を利用する技術がめざましく進歩し、これまでに気体や液体の分離フィルター、医療分野における血液透析器、血液濾過器、血液成分選択分離フィルター等の広範な分野での

実用化が進んでいる。該膜の材料としては、セルロース系（再生セルロース系、酢酸セルロース系、化学変性セルロース系等）、ポリアクリロニトリル系、ポリメチルメタクリレート系、ポリスルホン系、ポリエチレンビニルアルコール系、ポリアミド系等のポリマーが用いられてきた。このうちポリスルホン系ポリマーは、その熱安定性、耐酸、耐アルカリ性に加え、製膜原液に親水化剤を添加して製膜することにより、血液適合性に向うことから、半透膜素材として注目され研究が進められてきた。

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【0003】 一方、膜を接着してモジュールを製作するためには膜を乾燥させる必要があるが、有機高分子よりなる多孔膜、なかでもポリスルホン系等の疎水性ポリマーからなる透析膜、限外濾過膜は、製膜後に乾燥させると乾燥前に比べ著しく透水量が低下することが知られている。そのため膜は常に湿潤状態か、水に浸漬させた状態で取り扱う必要があった。

【0004】 この対策として従来よりとられてきた方法は、製膜後、乾燥前にグリセリン等の低揮発性有機液体を多孔膜中の空孔部分に詰めておくことであった。しかしながら、低揮発性有機液体は、一般に高粘度なため、洗浄除去に時間がかかり、膜をモジュール成型して洗浄後も微量ではあるが低揮発性有機液体由来の溶出物等（低揮発性有機液体と化学反応して生成した様々な誘導体）がモジュール封入液中にみられることに問題があった。

【0005】 低揮発性有機液体を用いずに乾燥させる方法として、特許文献1には、低揮発性有機液体の代わりに塩化カルシウム等の無機塩を用いる方法が示されているが、洗浄除去する必要性に変わりはない。また、微量であるとしても残存した無機塩が透析患者に与える悪影響が危惧される。

【0006】 また、膜の乾燥方法として、特許文献2には、中空糸膜に対し水蒸気による湿熱処理を行ないながらマイクロ波を照射する中空糸膜の製造方法が示されている。しかし、乾燥でありながら膜の変形を防ぐために水蒸気処理していることから乾燥時間を長くする欠点があり、さらに、グリセリン等の低揮発性有機液体を付着させてからの乾燥であることから、膜からの溶出物を低減させるという目的は達成されない。

【0007】 特許文献3及び特許文献4には、低揮発性有機液体を用いずに乾燥処理をしたポリビニルピロリドンを含む親水化膜が開示されている。これらには、血液から血漿成分を分離する性能が記載されているが、血漿タンパクが透過することから透析膜としては有効でないことが分かる。また、ポリビニルピロリドンを分解・変性させる温度で乾燥していることから、膜からの溶出物を低減するという目的においては極めて好ましくない製法である。

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【0008】 また、特許文献5には血液が直接接する

膜内表面でのポリビニルピロリドンの存在率を20〜50%程度にした中空糸膜が開示されている。これは主に血液タンパク、血小板等の附着物を少なくするための湿潤膜を示すものである。従って、血液タンパクが附着しにくいことからろ液速度の経時変化が起りにくいことが示されているが、アルブミンの透過性が低い等の透析性能についての記載は一切無い。

【0009】本発明者は、特定の性能を有する湿潤膜をグリセリン等の低揮発性有機液体に含浸せずに乾燥して高性能な血液浄化膜を製造する方法を提案した(特許文献6)が、糸束状にして乾燥した場合、糸束の中心部と外周部の膜とでは若干の性能差が生じることが明らかとなった。

【0010】

【特許文献1】特開平6-277470号公報

【特許文献2】特開平11-332980号公報

【特許文献3】特開平8-52331号公報

【特許文献4】特公平8-9668号公報

【特許文献5】特開平6-296686号公報

【特許文献6】特許第3281364号公報

【0011】

【発明が解決しようとする課題】本発明の課題は、膜からの溶出量が極めて少なく、血液タンパク質や血小板の附着が少ない優れた中空糸状膜の製造方法において、特に透水量及び透過率等の性能のばらつきを小さな中空糸状膜を製造する方法を提供することにある。また、本発明の課題は、透水性及び透過率などの性能が中心部と外周部とでばらつきがないモジュールを提供することにも関する。

【0012】

【課題を解決するための手段】以上の如くモジュールからの溶出物の原因となる膜孔保持剤を用いずに乾燥した透析性能を有する血液浄化用乾燥膜は本発明者等の出願発明(特許文献6)までなかった。その原因は、膜孔保持剤を用いずに乾燥させたこと、湿潤状態とは全く異なった低性能の膜となることであった。そこで、本発明者等は、前期出願により、あらかじめ目標とする性能よりも高透水量で大孔径である特定の性能を有する湿潤膜を作製しておき、これを乾燥・収縮させて目標の透析性能を有する膜を製造するというこれまでにない、誰も思いつかなかった発想に基づき鋭意研究を進めた結果、溶出物が極めて少なく、血液タンパクや血小板の附着が少ない選択透過性に優れた透析性能を有する膜を得る方法を提供した。その後、さらに研究を進めたこと、本発明者らは、特許文献6の方法によって血液浄化膜を製造する際、湿潤膜を糸束状にして乾燥すると、糸束の中心部と外周部の膜とでは、透水量や透過性能にばらつきが生じることを発見した。そこで、ばらつきをなくすために鋭意研究した結果、乾燥工程を工夫することで、ばらつきが抑えられることを見出し本発明に至ったものである。

【0013】すなわち本発明は、ポリスルホン系ポリマーとポリビニルピロリドンからなる、高透水量で大きな孔径の膜孔保持材を含まない湿潤膜をあらかじめ製造しておき、脱溶剤後乾燥することにより該湿潤膜の孔径を収縮させた後、さらに膜中のポリビニルピロリドンの一部を水に不変化する工程を含む、溶出物の少ない乾燥した中空糸状膜を製造する方法において、湿潤膜の乾燥工程をマイクロ波照射によって行うことを特徴とする中空糸状膜の製造方法に関するものである。

【0014】本発明では、また、乾燥するとき、中空糸状膜を糸束状に束束して、該糸束内に除湿気体を通過することが好ましい。本発明では、乾燥開始時に糸束の中心部と外周部における膜の含水率の差を10%以内に少なくしておくことが、さらに好ましい。

【0015】さらに、本発明は、乾燥開始後の糸束の含水率が20〜70%になる時点でマイクロ波照射の出力を低下させるか、あるいはマイクロ波照射乾燥から40℃以上120℃以下の温度の加熱乾燥に切り替える方法に関するものである。その際、乾燥開始後の糸束の含水率が20〜70%になる時点で該糸束の中心部と外周部における膜の含水率の差が5%以内であることが、さらに好ましい。上記の方法において、製膜原液が、ポリスルホン系ポリマー、ポリビニルピロリドン、及び溶剤からなり、ポリスルホン系ポリマーに対するポリビニルピロリドンの比率が18〜27重量%であることが好ましい。本発明は、また、上記のように製造された中空糸状膜からなるモジュールにも関するものである。本発明の中空糸状膜は血液透析性能に優れており血液透析のための中空糸状膜として用いられる。さらに、その他の体外循環治療のための膜としても有用である。

【0016】

【発明の実施の形態】以下に、本発明の中空糸状膜(以下単に「膜」ともいう)の構成について説明する。本発明の製造方法は、高透水量で大きな孔径の湿潤膜をあらかじめ製造しておき、脱溶剤後に膜孔保持剤を含浸させずに乾燥させることに特徴を有する。

【0017】通常、中空糸状膜を製造する際に用いられる膜孔保持剤には、粘性を有する有機物と人体への毒性が懸念される無機物に分類される。粘性を有する有機物からなる膜孔保持剤は、粘性が高いために完全に洗浄除去することが困難であることから、膜に残存して膜からの溶出量を増加させ、さらに残存した膜孔保持剤と化学反応して有害物を生じる原因となり得る。一方、無機物からなる膜孔保持剤においても、微量に残存するため透析患者に与える悪影響が危惧される。

【0018】本発明でいう膜孔保持剤とは、乾燥時の性能低下を防ぐために乾燥前までの製造過程で膜中の空洞部分に詰めておく物質である。膜孔保持剤を含んだ溶液に湿潤膜を浸漬することによって膜中の空洞部分に該保持剤を詰めることが可能である。乾燥後も膜孔保持剤を

洗浄・除去さえすれば、膜孔保持剤の効果により湿潤膜と同等の透水量、阻止率等の性能を保持することが可能である。

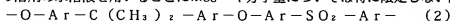
【0019】膜孔保持剤としては、エチレングリコール、プロピレングリコール、トリメチレングリコール、1, 2-ブチレングリコール、1, 3-ブチレングリコール、2-ペンチン-1, 4-ジオール、2-メチル-2, 4-ペンタジオール、2-エチル-1, 3-ヘキサジオール、グリセリン、テトラエチレングリコール、ポリエチレングリコール200、ポリエチレングリコール300、ポリエチレングリコール400等のグリコール系又はグリセロール系化合物及び蔗糖脂肪酸エステル等の有機化合物および塩化カルシウム、炭酸ナトリウム、酢酸ナトリウム、硫酸マグネシウム、硫酸ナトリウム、塩化亜鉛等の無機塩を挙げることができる。

【0020】また、本発明において、高透水量で大きな\*

$$\text{透過率}(\%) = (\text{濾液の吸光度}) \times 100 / (\text{元液の吸光度}) \quad (1)$$

【0022】ポリビニルピロリドンの透過率は、濾過する水溶液を3重量%のポリビニルピロリドン(BASF社製K30、重量平均分子量40,000)の1%水溶液にして、モジュールの入り圧と出圧の平均圧力を200mmHgにした以外は、牛血漿アルブミンの透過率の測定と同様な操作を行うことにより求められる。

【0023】高透水量で大きな孔径の湿潤膜は、ポリスルホン系ポリマー(以下単に「ポリマー」ともいう)、ポリビニルピロリドン、及び溶剤からなる製膜原液を、内部液とともに2重環状ノズルから吐出させ、エアギャップを通過させた後、凝固浴で凝固させる製造方法において、内部液にポリマーの溶剤の水溶液を用いることに※30



【0026】ポリビニルピロリドンは高分子量のものほど膜への親水化効果が高いため、高分子量のものほど少量の範囲で効果が発揮できることから、本発明においては重量平均分子量900,000以上のポリビニルピロリドンが使用される。900,000より小さい重量平均分子量を有するポリビニルピロリドンを用いて膜への親水化効果を付与するためには大量のポリビニルピロリドンを膜中に残存させる必要があるが、このために膜からの溶出物が増加することになる。また、逆に溶出物を下げるために900,000より小さい重量平均分子量のポリビニルピロリドンの膜中での残存量を少なくすると親水化効果が不十分となってしまう、その結果血液透析を行ったとき濾過速度の経時的低下をきたし十分な効果を発揮できない。

【0027】また、ポリスルホン系ポリマーとポリビニルピロリドンの溶解に用いられる溶剤は、これら両方を共に溶解するものであり、N-メチル-2-ピロリドン、N,N-ジメチルホルムアミド、N,N-ジメチルアセトアミド等である。

\* 孔径の湿潤膜とは、透水量が $100\text{mL}/(\text{m}^2 \cdot \text{hr} \cdot \text{mmHg})$ 以上であって、重量平均分子量40,000のポリビニルピロリドンの透過率が75%を超え、かつ牛血漿系におけるアルブミンの透過率が0.3%以上である性能を有する湿潤膜を意味する。

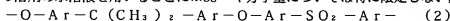
【0021】牛血漿アルブミンの透過率は、以下のような方法で測定することが可能である。まず、長さ20cmの中空糸状膜を100本束ねて小型モジュールを製作する。このモジュールに37℃に加熱したヘパリン添加牛血漿(ヘパリン5000IU/L(リットル)、タンパク濃度6.0g/dL(デシリットル))を膜内表面側に線速1.0cm/秒で通過させ、モジュールの入り圧と出圧の平均圧力50mmHgにて30分間隔で濾過を行う。得られた濾液と元液の濃度の測定は、紫外分光光度計により280nmの波長にて測定し、下記の式(1)に代入して透過率を算出する。

$$\text{透過率}(\%) = (\text{濾液の吸光度}) \times 100 / (\text{元液の吸光度}) \quad (1)$$

※より製造可能である。

【0024】内部液は、膜の中空部と内表面を形成させるものであるが、内表面の孔径は、内部液中の溶剤濃度に比例して大きくなることが判っている。本発明では、湿潤膜を乾燥収縮させることにより目標の性能の透析膜が得られることから、内部液中の溶剤濃度を、目標とする透析性能を有する湿潤膜を製造する時に比べて、高濃度にする必要がある。

【0025】本発明で用いられるポリスルホン系ポリマーとしては、下記の式(2)、または式(3)で示される繰り返し単位を有するものが挙げられる。なお、式中のArはパラ位の2置換のフェニル基を示し、重合度や分子量については特に限定しない。



【0028】製膜原液中のポリマー濃度は、製膜可能で、かつ得られた膜が膜としての性能を有するような濃度の範囲であれば特に制限せず、5~35重量%、好ましくは10~30重量%である。高い透水性能を達成するためには、ポリマー濃度は低い方がよく、10~25重量%が好ましい。

【0029】さらに重要なことはポリビニルピロリドンの添加量であり、ポリマーに対するポリビニルピロリドンの混和比率が27重量%以下、好ましくは10~27重量%、さらに好ましくは20~27重量%である。ポリマーに対するポリビニルピロリドンの混和比率が27重量%を超えると溶出量が増える傾向にあり、また10重量%未満では製膜原液の粘性が低いためにスポンジ構造の膜を得ることが困難である。また、原液粘度、溶解状態を制御する目的で、水、貧溶剤等の第4成分を添加することも可能であり、その種類、添加量は組み合わせにより随時行えばよい。

【0030】凝固浴としては、例えば水；メタノール、

エタノール等のアルコール類；エーテル類； $n$ -ヘキサン、 $n$ -ヘプタン等の脂肪族炭化水素類などポリマーを溶解しない液体が用いられるが、水が好ましい。また、凝固浴にポリマーを溶解する溶剤を若干添加することにより凝固速度をコントロールすることも可能である。

【0031】凝固浴の温度は、 $-30\sim 90^{\circ}\text{C}$ 、好ましくは $0\sim 90^{\circ}\text{C}$ 、さらに好ましくは $0\sim 80^{\circ}\text{C}$ である。凝固浴の温度が $90^{\circ}\text{C}$ を超えたり、 $-30^{\circ}\text{C}$ 未満であること、凝固浴中の中空糸状膜の表面状態が安定しにくい。

【0032】脱溶剤洗浄後の乾燥は、中空糸状膜を多数本束ねた糸束の形態（以後、単に『糸束』と呼ぶ）にて、十分に湿潤している糸束にマイクロ波を照射することにより行なわれる。

【0033】しかしながら、マイクロ波照射は低含水率の糸束をより均一に乾燥するのに適していることから、過加熱による膜の変形・熔融を防ぐために、糸束の平均含水率が $20\sim 70\%$ 、より好ましくは $50\sim 70\%$ になる時点でマイクロ波照射の出力を低下させるのが好ましい。

【0034】さらに、糸束の平均含水率が $20\sim 70\%$ 、好\*

$$\text{含水率}(\%) = (A-B) \times 100 / B \quad (4)$$

【0036】さらに、糸束の中心部と外周部の乾燥速度の差をなくすために、糸束内には $40^{\circ}\text{C}$ を超えない温度の除湿気体を流通することが好ましい。糸束内に流通するとは中空糸状膜間に風を流すことを意味する。本発明において、 $40^{\circ}\text{C}$ 以上 $120^{\circ}\text{C}$ 以下の温度の除湿気体を糸束内に流通することは、糸束内に流通すると同時に糸束に対し加熱乾燥を行っていることを意味する。

【0037】マイクロ波の出力は高いことが好ましいが、乾燥させる膜の量により最適値は異なる。また、糸束の含水率が $20\sim 70\%$ 、好ましくは $50\sim 70\%$ になる時点でマイクロ波照射から $40^{\circ}\text{C}$ 以上 $120^{\circ}\text{C}$ 以下の温度の送風乾燥に切り替える2段階乾燥を行う方法でも、マイクロ波照射よりは乾燥時間を要するが、糸束を均一に乾燥することが可能である。2段階乾燥法においても、糸束の含水率が $20\sim 70\%$ 、好ましくは $50\sim 70\%$ になる時点で該糸束の中心部と外周部における膜の含水率の差が $5\%$ 以内であることが性能のばらつきを抑えるのに有効である。

【0038】加熱乾燥の温度は、 $40^{\circ}\text{C}$ 以上 $120^{\circ}\text{C}$ 以下であることが好ましく、さらに好ましくは $100^{\circ}\text{C}$ 以下である。 $120^{\circ}\text{C}$ を超えるとポリビニルピロリドンが変性および分解するために、膜孔保持剤を用いなくても得られた乾燥膜からの溶出量が増えることから好ましくない。また、 $40^{\circ}\text{C}$ 未満では、乾燥時間がかかり過ぎるのが好ましくない。

【0039】乾燥後の膜に電子線及び $\gamma$ 線等の放射線を照射することにより、膜中のPVPの一部を水に不溶化できることから、膜からの溶出量をより低減することが可能である。放射線の照射は、モジュラー化前又はモジュラー化後のどちらでも良い。また、膜中の全PVPを不溶

\* ましくは $50\sim 70\%$ になる時点で該糸束の中心部と外周部における膜の含水率の差が $5\%$ 以内であることが、性能のばらつきを抑えるためにより好ましい。乾燥の時、糸束内に通風を行うことによって、糸束の中心部と外周部における膜の含水率の差を $5\%$ 以内にするのが可能である。ここで、糸束の中心部とは、糸束の円形状断面において中心点から直径の $1/6$ の範囲をいう。また、糸束の外周部とは、糸束の円形状断面において外周から $1/6$ の範囲をいう。

【0035】また、同様な理由から、乾燥開始時における糸束についても、糸束の中心部と外周部における膜の含水率の差が $10\%$ 以内であることが好ましい。脱溶剤後糸束を放置しておくこと、乾燥の中心部と外周部の含水率には差が生じるために、乾燥工程に入る直前に糸束を再度水中に浸漬することにより糸束中心部と外周部の含水率の差を $10\%$ 以内にするのが可能である。ここで、含水率とは、乾燥前の糸束（又は膜）の重量（A（g））と乾燥糸束（又は膜）の重量（B（g））から（4）式により計算で求められるものをいう。

化してしまうと、溶出量を低減できる一方で、透析時に口コペニア症状が観察されることが好ましくない。【0040】本発明でいう水に不溶であるPVPとは、膜中の全PVP量から水に可溶であるPVP量を差し引いたものである。膜中の全PVP量は、窒素及びイオンの元素分析により容易に算出することができる。また、水に可溶であるPVP量は、以下の方法により求めることができる。

膜をN-メチル-2-ピロリドンで完全に溶解した後、得られたポリマー溶液に水を添加してポリスルホン系ポリマーを完全に沈殿させる。さらに該ポリマー溶液を静置した後、上澄み液中のPVP量を液体クロマトグラフィーで定量することにより水に可溶であるPVPを定量することができる。

【0041】本発明の製造方法は、膜孔保持剤を含まない湿潤膜をマイクロ波照射により乾燥することを特徴とし、本製造方法を用いて得られた膜は、膜孔保持剤を含まない乾燥膜であって、純水の透過量が $10\sim 1,000\text{mL}/(\text{m}^2 \cdot \text{hr} \cdot \text{mmHg})$ 、重量平均分子量40,000のポリスルホン系ポリロンドンの透過率が $5\%$ 以下で、且つ牛血漿系におけるアルブミンの透過率が $0.3\%$ 未満であり、さらにそれぞれの性能のパラッキが小さいことを特徴とする中空糸状膜である。最近の血液透析療法では、透析アミロイド病状の改善のために原因物質とされている $\beta_2$ -ミクログロブリン（分子量：11,800）を十分に透過させるが、アルブミン（分子量：67,000）はほとんど透過させない分離性を有する膜が求められており、本発明の膜は、牛血漿系におけるアルブミンの透過率が $0.3\%$ 以下である。アルブミンの透過率が $0.3\%$ を超えることは体内に有効なアルブミンを大きく損失することを意味することから透析膜としては好ましくない。

$$B \text{ (mL/分)} = 0.636A + 29.99$$

【0044】また、本発明の製造方法により作られた膜は、膜孔保持剤を製造工程で使用しないことから、膜孔保持剤由来の溶出物は存在しない。従って、本発明の膜の溶出物試験液の吸光度は0.04未満であり、且つ該試験液中に腎臓保持剤を含まない。ここで、溶出物試験液とは、人工腎臓装置承認基準に基づき調整したものであり、2cm<sup>2</sup>以下サイズの乾燥中空糸状膜1.5gと注射用蒸留水150mLを日本薬局方の注射用ガラス容器試験のアルカリ溶出試験に適合するガラス容器に入れ、70±5℃で1時間加熱し、冷却後膜を取り除いた後蒸留水を加えて150mLとしたものを意味する。吸光度は220~350nmでの最大吸収波長を示す波長にて紫外吸収スペクトルで測定する。人工腎臓装置承認基準では吸光度を0.1以下にすることが定められているが、本発明の膜は膜孔保持剤を保持しないことから0.04未満を達成することが可能である。また、膜孔保持剤の有無については、該試験液を濃縮又は水分除去したものをガスクロマトグラフィー、液体クロマトグラフィー、示差折光法、紫外分光分析計、赤外線吸収光度法、核磁気共鳴法、及び元素分析計等※

【0047】

(血小板粘着量の測定) 膜への血小板粘着量の測定は、以下の操作手順で行った。長さ15cmの中空糸状膜を100本束ねて小型モジュールを作製し、該モジュールにヘパリン添加ヒト新鮮血を線速1.0cm/秒にて15分間通過させ、続いて生理食塩水を1分間通過させた。次に中空糸

【0046】膜内表面のPVP濃度は、エックス線光量子スペクトル(X-ray Photoelectron spectroscopy,以下XPS)によって決定される。すなわち、膜内表面のXPSの測定は、試料を両面テープに貼った後、カッターで縦維軸方向に切開し、膜の内側に表になるように押し広げた後、通常の方法で測定する。すなわち、C1s, O1s, N1s, S2pを用いた面の面積強度から、装置付属の相対感度係数を用いて窒素の表面濃度(窒素原子濃度)とイオウの表面濃度(イオウ原子濃度)から求めた濃度をいうものであり、ポリスルホン系ポリマーが(2式)の構造であるときには(6式)により計算で求めることができる。

状態を5mm間隔程度に細断し、0.5%ポリエチレングリコールカルブエチルエーテル（和光純薬社製 商品名トリトン-X100）を含む生理食塩水中で超音波照射して膜表面に粘着した血小板から放出される乳酸脱水素酵素（以下、「LDH」という）を定量することにより膜面積（内表面換算）当たりのLDH活性として算出した。酵素活性の測定はLDHモノテストキット（ペーリンガー・マンハイム・社・之内社製）を使用した。なお、陽性対照としてPVPを含有しない膜（γ線照射前の実施例1）の膜を有効塩素濃度1,500ppmの次亜塩素酸ナトリウムに2日間浸漬した後、エタノールに1日間浸漬することにより得られたものを用い、試験品と同時に比較した。

【0048】(血漿タンパク質吸着量) 膜への血漿タン

パク質吸着量は、限外濾過時間を240分にした以外はアルブミンの透過率測定と同様な操作を行った後、生理食塩水で1分間洗浄した。次に中空糸状膜を5mm間隔程度に細断し、1.0%ラウリル硫酸ナトリウムを含む生理食塩水中で攪拌して抽出した血漿タンパク質を定量することにより膜重量当たりのタンパク質吸着量として算出した。タンパク質濃度はBCAプロテインアッセイ（ピアース製）を使用した。なお、陽性対照としてPVPを含有しない膜（γ線照射前の実施例1の膜を有効塩素濃度1,500ppmの次亜塩素酸ナトリウムに2日間浸漬した後、エタノールに1日間浸漬することにより得られたもの）を用い、試験品と同時に比較した。

#### 【0049】

【実施例1】（製膜及び残溶剤の除去）ポリスルホン（Amoco Engineering Polymers社製 P-1700）18.0重量%、ポリビニルピロリドン（BASF社製 K90、重量平均分子量1,200,000）4.3重量%を、N,N-ジメチルアセトアミド77.7重量%に溶解して均一な溶液とした。ここで、製膜原液中のポリスルホンに対するポリビニルピロリドンの混和比率は23.9重量%であった。この製膜原液を20℃に保ち、N,N-ジメチルアセトアミド30重量%と水70重量%の混合溶液からなる内部液とともに、紡口（2重環状ノズル 0.1mm-0.2mm-0.3mm）から吐出させ、0.96mのエアギャップを通過させて75℃の水からなる凝固浴へ浸漬した。この時、紡口から凝固浴までを円筒状の筒で囲み、筒の中に水蒸気を含んだ窒素ガスを流しながら、筒の中の湿度を54.5%、温度を51℃にコントロールした。紡速は、80m/分に固定した。ここで、紡速に対するエアギャップの比率は、0.012m/（m/分）であった。巻き取った糸束を切断後、糸束（長さ300mm、膜本数9200本）の切断面上方から80℃の熱水シャワーを2時間かけて洗浄することにより膜中の残溶剤を除去した。

【0050】（湿潤膜の乾燥及びPVPの不溶化処理）上記の残溶剤除去後の糸束（含水率が300%、糸束中心部の膜の含水率が300%、糸束外周部の膜の含水率が300%、糸束の中心部と外周部における膜の含水率の差が0%）30本を21分間マイクロ波照射（出力30kW）した。この時点で、糸束の含水率は65%（糸束中心部の膜の含水率が65%、糸束外周部の膜の含水率が65%、糸束の中心部と外周部における膜の含水率の差が0%）であった。引き続いて、出力を落として4分間マイクロ波照射（出力21kW）することにより含水率が1%未満の乾燥膜（糸束）を得た。また、乾燥開始時から乾燥終了時までの間、各糸束の下部から8m/秒の風速にて除湿空気（湿度10%以下）を糸束の下部から上部へと通風した。この時、糸束の上部からは乾燥開始時において糸束平均で1m/秒の風速が測定された。さらに、得られた乾燥膜（糸束）に25kGyのγ線を照射することにより膜中のPVPの一部を不溶化した。

【0051】（性能評価結果）この膜の性能を表1に示

す。性能は10回測定した結果の平均値を示す。この膜を有効透過面積1.5m<sup>2</sup>のモジュールにしてβ<sub>2</sub>-ミクログロブリンのクリアランスを測定したところ、32mL/分であることが分り、PVPの透過率を式（6）に代入して算出したクリアランス32.5mL/分と同等であることが明らかとなった。さらに、該モジュールにて尿素、ビタミンB<sub>12</sub>の透過測定を行ったところ、尿素のクリアランスと透過率はそれぞれ185mL/分、48%であった。また、ビタミンB<sub>12</sub>については同様に95mL/分、48%であった。測定

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【0042】と同様な方法で行った。また、膜中の全PVP量の62%が、水に不溶であった。膜の溶出物試験をした結果、溶出物試験液の吸光度は0.04以下であった。また、膜孔保持剤を用いていないことから溶出物試験液中に膜孔保持剤は含まれて無かった。さらに、この膜は陽性対照膜に比べて、血小板粘着量が低く（陽性対照膜43.4Unit/m<sup>2</sup>）、且つ血漿タンパク質の粘着量も低いことが明らかとなった（陽性対照膜62.5mg/g）。

【0052】以上に挙げた性能から、この膜は、膜からの溶出量が極めて少なく、血液タンパク質や血小板の付着が少ないことが明らかとなった。また、アルブミンの透過率が少なくβ<sub>2</sub>-ミクログロブリンのクリアランスにも優れることから透析性能にも優れた膜であることが分かった。さらに、糸束の中心部と外周部における膜の性能の差がこれまでの乾燥方法（比較例1）に比べて少ないことから性能のばらつきが少ないことが明らかとなった。

#### 【0053】

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【実施例2】製膜原液中のポリビニルピロリドンを4重量%、N,N-ジメチルアセトアミドを78重量%とした以外は、実施例1と同様な操作を行った。この時の製膜原液中のポリスルホンに対するポリビニルピロリドンの混和比率は22.2重量%であった。この膜の性能を表1に示す。この膜は、膜からの溶出量が極めて少なく、血液タンパク質や血小板の付着が少ないことが明らかとなった。また、アルブミンの透過率が少なく、且つβ<sub>2</sub>-ミクログロブリンのクリアランスにも優れることが示唆されたことから透析性能にも優れた膜であることが分かった。さらに、糸束の中心部と外周部における膜の性能の差がこれまでの乾燥方法（比較例1）に比べて少ないことから性能のばらつきが少ないことが明らかとなった。

#### 【0054】

【実施例3】製膜原液中のポリビニルピロリドンを4.8重量%、N,N-ジメチルアセトアミドを77.2重量%とした以外は、実施例1と同様な操作を行った。この時の製膜原液中のポリスルホンに対するポリビニルピロリドンの混和比率は26.7重量%であった。この膜の性能を表1に示す。この膜は、膜からの溶出量が極めて少なく、血液タンパク質や血小板の付着が少ないことが明らかとなった。また、アルブミンの透過率が少なく、且つβ<sub>2</sub>-

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ミクログロブリンのクリアランスにも優れることが示唆されたことから透析性能にも優れた膜であることが分かった。さらに、糸束の中心部と外周部における膜の性能の差がこれまでの乾燥方法（比較例1）に比べて少ないことから性能のばらつきが少ないことが明らかとなった。

#### 【0055】

【実施例4】内部液にN,N-ジメチルアセトアミド52重量%と水48重量%からなる混和溶液を用いた以外は、実施例3と同様な操作を行った。この膜の性能を表2に示す。この膜は、膜からの溶出量が極めて少なく、血液タンパク質や血小板の付着が少ないことが明らかとなった。また、アルブミンの透過率が少なく、かつ $\beta_2$ -ミクログロブリンのクリアランスにも優れた膜であることが分かった。さらに、糸束の中心部と外周部における膜の性能の差がこれまでの乾燥方法（比較例1）に比べて少ないことから性能のばらつきが少ないことが明らかとなった。

#### 【0056】

【実施例5】残留溶剤除去後の糸束（含水率が300%、糸束中心部の膜の含水率が300%、糸束外周部の膜の含水率が300%、糸束の中心部と外周部における膜の含水率が0%）30本を21分間マイクロ波照射（出力30kW）した後、糸束の含水率が65%（糸束中心部の膜の含水率が65%、糸束外周部の膜の含水率が65%、糸束の中心部と外周部における膜の含水率の差が0%）であることを確認した後、87℃に設定した乾燥機（乾燥機内の循環風速3m/秒）に3時間入れることにより加熱乾燥して含水率が1%未満の糸束を得た以外は実施例1と同様な操作を行った。この膜の性能を表2に示す。この膜は、膜からの溶出量が極めて少なく、血液タンパク質や血小板の付着が少ないことが明らかとなった。また、アルブミンの透過率が少なく、かつ $\beta_2$ -ミクログロブリンのクリアランスにも優れることが示唆されたことから透析性能にも優れた膜であることが分かった。さらに、糸束の中心部と外周部における膜の性能の差がこれまでの乾燥方法（比較例1）に比べて少ないことから性能のばらつきが少ないことが明らかとなった。

#### 【0057】

【比較例1】残留溶剤除去後の糸束（含水率が300%、糸束中心部の膜の含水率が300%、糸束外周部の膜の含水率が300%、糸束の中心部と外周部における膜の含水率の差が0%）30本を、87℃に設定した乾燥機（乾燥機内の循環風速3m/秒）に7時間入れることにより加熱乾燥して含水率が1%未満の糸束を得た以外は実施例1と同様な操作を行った。この結果を表2に示す。透水量及PVPの透過率において糸束の中心部と外周部における膜の性

能に差があり、結果として糸束内で性能のばらつきがあることが明らかとなった。

#### 【0058】

【比較例2】 $\gamma$ 線照射しない以外は、実施例1と同様な操作を行った。この結果を表3に示す。PVPの溶出のため溶出試験液の吸光度が0.04を超えることが明らかとなった。

#### 【0059】

【比較例3】製膜原液中のポリビニルピロリドン5.0重量%、N,N-ジメチルアセトアミド77.0重量%とした以外は、実施例1と同様な操作を行った。この時の製膜原液中のポリスルホンに対するポリビニルピロリドンの混和比率は27.8重量%であった。この膜の性能を表3に示す。製膜原液中のポリスルホンに対するポリビニルピロリドンの混和比率が27重量%を超えているので、溶出量、膜内表面PVP濃度が増加している。

#### 【0060】

【比較例4】製膜原液中のポリビニルピロリドン3.6重量%、N,N-ジメチルアセトアミド78.4重量%とした以外は、実施例1と同様な操作を行った。この時の製膜原液中のポリスルホンに対するポリビニルピロリドンの混和比率は20.0重量%であった。この膜の性能を表3に示す。膜内表面のPVP量が30%を下回っていることが明らかとなった。

#### 【0061】

【比較例5】内部液にN,N-ジメチルアセトアミド60重量%と水40重量%からなる混和溶液を用いた以外は、実施例3と同様な操作を行った。この膜の性能を表3に示す。この膜は、アルブミンの透過率が0.3%を超えており、またPVPの透過率も75%を超える性能であった。

#### 【0062】

【比較例6】内部液にN,N-ジメチルアセトアミド10重量%と水90重量%からなる混和溶液を用いた以外は、実施例1と同様な操作を行った。この膜の性能を表3に示す。純水の透水量が10mL/( $\text{m}^2 \cdot \text{hr} \cdot \text{mmHg}$ )を下回る性能であった。

#### 【0063】

【比較例7】乾燥温度を170℃にした以外は、実施例1と同様な操作を行った。この膜の性能を表3に示す。この膜は、膜中の全てのPVPが水に不溶であった。この膜を有効濾過面積1.5 $\text{m}^2$ のモジュールにして血液流量200mL/分（膜内表面側）、透析液流量500mL/分（膜外表面側）の条件下で日本人工臓器学会の性能評価基準に従い臨床血液評価したところ、透析患者の白血球数が一時的に低下するロイコペニア症状が観察された。

#### 【0064】

【表1】

	実施例1		実施例2		実施例3	
	糸束中心部	糸束外周部	糸束中心部	糸束外周部	糸束中心部	糸束外周部
膜内径( $\mu\text{m}$ )	195	195	201	201	190	190
膜外径( $\mu\text{m}$ )	280	280	288	288	282	282
透水量( $\text{mL}/(\text{m}^2 \cdot \text{hr} \cdot \text{mmHg})$ )	20	20	19	18	25	25
アルブミンの透過率(%)	0.01以下	0.01以下	0.01以下	0.01以下	0.01以下	0.01以下
PVPの透過率(%)	4	4	4	4	5	5
膜内表面PVP濃度(重量%)	35	35	30	30	44	44
水に不溶であるPVPの有無	有り	有り	有り	有り	有り	有り
溶出物試験液の吸光度	0.022	0.022	0.020	0.020	0.035	0.035
溶出物試験液中の膜孔保持剤の有無	無し	無し	無し	無し	無し	無し
血小板粘着量( $\text{LDH-Unit}/\text{m}^2$ )	15.5	15.5	17.5	17.5	4.2	4.2
血漿タンパク質吸着量( $\text{mg}/\text{g}$ )	2.1	2.1	5.5	5.5	1.8	1.8
乾燥前滲透膜の透水量( $\text{mL}/(\text{m}^2 \cdot \text{hr} \cdot \text{mmHg})$ )	190	190	170	170	260	260
乾燥前滲透膜のアルブミンの透過率(%)	0.32	0.32	0.34	0.34	0.35	0.35
乾燥前滲透膜のPVPの透過率(%)	77	77	84	84	84	84

【0065】

【表2】

	実施例4		実施例5		比較例1	
	糸束中心部	糸束外周部	糸束中心部	糸束外周部	糸束中心部	糸束外周部
膜内径( $\mu\text{m}$ )	194	194	196	195	195	195
膜外径( $\mu\text{m}$ )	284	284	280	280	281	280
透水量( $\text{mL}/(\text{m}^2 \cdot \text{hr} \cdot \text{mmHg})$ )	390	390	22	20	28	20
アルブミンの透過率(%)	0.25	0.25	0.01以下	0.01以下	0.01以下	0.01以下
PVPの透過率(%)	72	72	4	4	8	4
膜内表面PVP濃度(重量%)	36	36	35	35	35	35
水に不溶であるPVPの有無	有り	有り	有り	有り	有り	有り
溶出物試験液の吸光度	0.023	0.023	0.022	0.022	0.022	0.022
溶出物試験液中の膜孔保持剤の有無	無し	無し	無し	無し	無し	無し
血小板粘着量( $\text{LDH} \cdot \text{Unit}/\text{m}^2$ )	13.8	13.8	15.6	15.5	15.6	15.5
血漿タンパク質吸着量( $\text{mg}/\text{g}$ )	2.0	2.0	2.1	2.1	2.1	2.1
乾燥前湿潤膜の透水量( $\text{mL}/(\text{m}^2 \cdot \text{hr} \cdot \text{mmHg})$ )	3100	3100	190	190	190	190
乾燥前湿潤膜のアルブミンの透過率(%)	0.51	0.51	0.32	0.32	0.32	0.32
乾燥前湿潤膜のPVPの透過率(%)	99	99	77	77	77	77

【0066】

【表3】

	比較例 2	比較例 3	比較例 4	比較例 5	比較例 6	比較例 7
	糸束外周部	糸束外周部	糸束外周部	糸束外周部	糸束外周部	糸束外周部
膜内径 ( $\mu\text{m}$ )	195	200	199	196	200	191
膜外径 ( $\mu\text{m}$ )	290	298	290	297	291	276
透水量 ( $\text{mL}/(\text{m}^2 \cdot \text{hr} \cdot \text{mmHg})$ )	20	35	15	970	8	15
アルブミンの透過率 (%)	0.01 以下	0.01 以下	0.01 以下	0.37	0.01 以下	0.01 以下
PVP の透過率 (%)	4	5	4	79	0	4
膜内表面 PVP 濃度 (重量%)	35	47	28	33	34	36
水に不溶である PVP の有無	無し	有り	有り	有り	有り	有り
溶出物試験液の吸光度	0.044	0.040	0.018	0.021	0.020	0.021
溶出物試験液中の膜孔保持剤の有無	無し	無し	無し	無し	無し	無し
血小板粘着量 ( $\text{LDH} \cdot \text{Unit}/\text{m}^2$ )	15.5	3.8	19.6	15.0	15.1	16.8
血漿タンパク質吸着量 ( $\text{mg}/\text{g}$ )	2.1	1.1	5.9	2.8	2.1	3.0
乾燥前湿潤膜の透水量 ( $\text{mL}/(\text{m}^2 \cdot \text{hr} \cdot \text{mmHg})$ )	190	310	130	8600	76	190
乾燥前湿潤膜のアルブミンの透過率 (%)	0.32	0.38	0.31	0.62	0.18	0.32
乾燥前湿潤膜の PVP の透過率 (%)	77	85	76	100	52	77

【0067】

\* 透析性能を有することから医薬用途、医療用途、及び一

【発明の効果】本発明の膜は、膜からの溶出量が極めて 30 般工業用途に用いることができる。  
 少なく、血液タンパク質や血小板の付着が少ない優れた \*

フロントページの続き

(51)Int.Cl.<sup>7</sup>

識別記号

F I

テマコード (参考)

B O I D 71/44  
71/68B O I D 71/44  
71/68

F ターム (参考) 4D006 GA13 HA01 MA01 MA21 MB02  
 MB06 MB18 MC21X MC62X  
 NA13 NA17 NA18 NA50 NA60  
 NA64 PB09 PB52